

# **A CLINICAL ASSESSMENT OF ORPHENADRINE (DISIPAL) IN THE TREATMENT OF PARKINSONISM**

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PSYCHOLOGICAL medicine is today emerging from an isolation born of neglect and the importance of its contribution to scientific knowledge is becoming increasingly recognised. More and more emphasis is being laid on its integration into the field of general medicine and the psychiatrist today is as much a physician of body as of mind. In no aspect of medicine is this more evident than in the elder science of neurology where the psychiatrist and physician meet on familiar ground to study different aspects of the same problems. One of these problems is the treatment of those patients who suffer from what is commonly called Parkinsonism, where the mental concomitants include depression which is often severe and delusional ideas. In a minority of cases the physical symptoms, especially tremor, can be alleviated by surgery or ultrasonic coagulation, but for the vast majority treatment depends upon the use of suitable drugs and compounds such as stramonium, artane and lysivane are commonly employed.

In the last few years attention has been drawn to a new drug called orphenadrine, marketed under the trade name of 'Disipal,' which showed great promise in treating cases of Parkinsonism. Certain special claims have been made for Disipal, one of which is that it possesses a euphoriant action which helps to relieve the depression so often associated with Parkinsonism—the so-called psycho-tonic effect. Chlorpromazine and various drugs of the phenothiazine series can be used in the treatment of schizophrenia, and in high dosage induce Parkinsonism symptoms. While the therapeutic value of this is still a very controversial subject, Disipal can be used to combat their unwanted side effects.

The aims of the present investigation were:—

1. To ascertain the efficacy of Disipal in controlling the symptoms of Parkinsonism: Tremor, rigidity, weakness, salivation, dysarthria and disturbances of gait.
2. To compare its efficiency with that of other commonly used drugs.
3. To study its effects, if any, on the mental concomitants of Parkinsonism especially depression.

## **PHARMACOLOGY.**

Disipal is related to diphenhydramine (Benadryl), differing from it by the substitution of a methyl group. Because of its formula Disipal might be expected to be an anti-histamine agent like Benadryl, but with the addition of the methyl

group the anti-histamine action has almost disappeared and has been replaced by a strong atropine-like effect, i.e., it antagonises acetyl choline. Bijlsma, et al. (1956), report the acute LD<sub>50</sub> dose in rats as 425 mgm. orally or 230 mgm. by subcutaneous injection.

The synthesis of this drug is a triumph for the research chemists because its action was predicted accurately by purely theoretical consideration from a knowledge of molecular structure. However, the actual translation of theory into reality took seven years and, after physiological assays and toxicity tests on experimental animals, it was finally handed over for evaluation by clinicians on suitable cases.

#### MATERIAL AND METHODS.

Twelve cases of Parkinsonism were selected—six male and six female. All were in-patients of a modern mental hospital and were under careful observation. The only criteria of selection were that they should be the worst cases and should have a marked tremor especially in the upper limbs. Their ages ranged between 41 and 62, and eleven were regarded as being post-encephalitic in origin. Their stay in hospital varied between four and twenty-nine years. All patients were mobile but five required continual assistance with dressing and eating. Their activities were restricted by their disabilities but most of them were able to walk for short distances in the immediate vicinity of their wards. Their physical condition varied only according to the amount of tremor and rigidity present. Four were subject to frequent and troublesome oculogyric crises. They were maintained on various combinations mainly of lysivane and stramonium. Two received lysivane, six lysivane and stramonium, three stramonium and one artane and stramonium.

Tremor was made one of the criteria because an apparatus was devised with which it was possible to measure the severity of the tremor with a fair degree of accuracy. It consists of an electrically-driven drum such as may be found in any physiology laboratory and which can revolve at different speeds, e.g., 5 or 11 rev./min. This drum carries a roll of ordinary graph paper and beside it is a vertical bar. To this bar is clamped at a variable position a strip of very thin flexible alloy shaped in the form of a right angle like the letter L and balanced around a small horizontal metal bar which acts as a fulcrum allowing the L piece to move in a vertical plane. At the tip of the horizontal limb is attached a tiny cup which serves as an ink reservoir. To the bottom of the vertical limb is fastened a ring lying in the horizontal plane. The patient places a finger or thumb in the ring and the tremor is transmitted through the fulcrum to the horizontal limb, causing a vertical movement of the ink cup and thus obtaining a tracing on the revolving drum. And so, in the most literal sense, the moving finger writes.

Every effort was made to standardise the variables involved. Thus the height of the ring above the table was constant for each patient on each occasion. The patient was placed at right angles to the apparatus as it was found that this gave maximum amplitude readings of flexion-extension movement which is the chief

component of Parkinsonian finger tremor. The patients were familiarised with the apparatus and procedure before commencing. Tracings were taken on three occasions:—

- (1) While on their original drugs.
- (2) After all drugs had been withdrawn.
- (3) After they had been receiving Disipal for about two months.

#### PROCEDURE OF TESTS.

Previous medicines were reduced gradually over a period of two-three weeks until at the end of this time the patients were not receiving any drugs whatsoever apart from occasional sedation at night. At this stage they all showed marked deterioration in their general condition as the full effects of the disease made itself felt. They all complained of weakness and objectively there was definite weakness, increased salivation and lachrymation and difficulty in articulation. They felt very miserable, lost interest in their former pastimes such as television, radio or reading, and had great difficulty in walking. Several of them retired to bed or lay on couches most of the day. A few patients showed increased excitability, became more irritable and noisy and oculogyric crises were more troublesome in the four cases prone to this disturbance.

Treatment was commenced with Disipal, giving one tablet of 50 mgms. morning and evening. This was continued for a week and the dosage was then increased by one tablet of 50 mgms. daily every four or five days. No cases of drug idiosyncrasy occurred. As dosages were increased two side effects made their appearance, namely, dizziness and blurred vision, which was reported by six patients. This occurred at dosage levels of four to seven tablets and disappeared within two days when the dose was reduced. In general the optimum dosage was found to be four to six tablets per day, i.e., 200-300 mgms.

#### RESULTS.

It was found that of the twelve patients eleven were restored to the same condition as while on their previous drugs or improved in various ways. One patient, a female, was not fully restored although improved in one respect, viz., articulation.

#### *Physical symptoms.*

The symptoms of the patients after their drugs had been removed have been described. When Disipal was given and the correct dosage found these symptoms were all remedied. Muscular strength was restored and the patients resumed their former interests and activities. To consider a few of the individual symptoms:—

1. Salivation: This was controlled in all cases.
2. Muscular strength: In eleven cases this was restored to its former level and apparently increased in three cases because these patients were able to walk for longer distances and perform tasks for longer periods without becoming fatigued.

3. Speech: Articulation was improved in four cases and this was noted not only by the ward staff but by the patients' relatives.
4. Tremor: Studies of the graphs showed that tremor amplitude was reduced in five cases, was unchanged in six, and was increased in one. There was no change in tremor frequency and the actual changes noted were seldom striking.

The above symptoms are all capable of objective study but cannot readily be expressed in scientific units. All comparisons are drawn with the patient's condition while on his former drugs.

At this point some sceptic may seek to suggest that all this could conceivably be psychological, that the improvement was in the mind and not the body. In order to settle this point identical placebo tablets were substituted to all patients—the only person who knew about this change being the dispensing chemist. This, of course, involved the innocent deception of the patients, the nursing staff and the medical staff in charge of the individual patients who were scattered throughout the hospital. The substitution was carried out on a Friday and by the following Monday or Tuesday all the patients were either in bed or on couches, weak and miserable with increased tremor and salivation. In other words the syndrome of untreated Parkinsonism had been unleashed again. The patients were miserable, the nurses were bewildered, and the doctors were perplexed. One patient interpreted the situation in a typically paranoid fashion and alleged that the nurses had poisoned his medicine. The tablets were called in immediately and genuine Disipal dispensed.

Within two days the situation had changed quite dramatically. Eleven patients were up and about and were able to resume their former activities. All their symptoms reverted to their usual base line. The exception to this was the single female patient mentioned earlier and there was no great change in her condition. This experience would seem to indicate that the improvement in the patients' condition was due to the drug and not to any psychological support.

#### *Mental state.*

According to their histories only one patient was subject to marked or sustained depression, the others being liable to patchy depression or changes of mood such as might be expected in people suffering from the illness. Irritability and aggression occurred from time to time. One patient had mild paranoid delusions.

When the original drugs were withdrawn ten of the patients became depressed in some degree, the other two being irritable and aggressive. Insomnia was marked. When they were stabilised on Disipal this depression disappeared (in eleven cases) and they all felt in normal spirits again. When placebo was introduced depression again recurred as deep and distressing as before and again was relieved when Disipal was given.

Depression is sometimes defined as a mood disturbance with a characteristically sorrowful affect—a somewhat tautological definition. If it is hard to define it

is even more difficult to measure. There have been various rating scales prepared with the object of measuring psychomotor activity but they were not considered to be suitable for the present circumstances. For the purposes of this investigation, if a patient was lying on a bed or couch apathetic and retarded and sometimes mentioning suicide with an appropriate affect, he was rated as being depressed.

#### DISCUSSION.

When receiving Disipal the depression was relieved. This immediately raises two questions:—

1. Were the patients more cheerful on Disipal than on other drugs?
2. If this is so, is it due to some specific euphoriant effect as claimed by some investigators?

To give a definite answer to these questions would require an objective scientific means of measuring small deviations of affect. From the subjective aspect five patients said that they felt better on Disipal than they had done on their previous medicines.

The claim that orphenadrine had a specific anti-depressive action was first advanced by Friesewinkel (1957). An examination of his report, however, shows that he bases his conclusions on the result of projective techniques. Professor Eysenck (1959), in his review of personality testing, makes it clear that such techniques lack validity and are not universally acceptable. Doshay and Constable (1957) report a euphoriant effect in thirty-one out of thirty-seven patients, while Robitscher and Pulver (1957) record a similar experience. Fouks, et al. (1959), noted that many of their patients felt better mentally even though sometimes they did not display much neurological improvement. A critical scrutiny of these reports, however, fails to show any series of controls or objective methods to prove specificity. No one as yet appears to have sought to show that the drug possesses anti-amine oxidase activity.

It seems more reasonable to suppose that a patient whose physical symptoms are controlled in a satisfactory manner will feel better as a result of this and to prove a specific euphoriant effect would require a separate carefully controlled trial on patients suffering from depression per se quite apart from Parkinsonism. If, however, a significant proportion of patients feel better on orphenadrine than on other drugs then due notice should be taken of this as a recorded fact and the accumulated experience of different investigators covering really large numbers of cases will give a good indication of its value.

The results given here are in general agreement with previous reports. Most of them, e.g., Berggreen (1958), emphasize the difficulties of accurate evaluation. Within the limitations outlined earlier it seems justifiable to draw the following conclusions:—

1. Orphenadrine controlled the effects of Parkinsonism in a satisfactory manner in eleven out of twelve of the patients in this series.

2. Side effects were confined to dizziness and blurred vision and these soon disappeared when the dosage was reduced. It appears to be a reasonably safe drug—no toxic effects were noted on kidneys or bone marrow, the blood picture remaining normal apart from very mild normocytic anæmia in a few cases. There was no sign of jaundice or liver damage.
3. The average dose was four to six tablets (200-300 mgms.).
4. As far as could be judged objectively the physical state of the patients in the majority of cases was at least as good as when they had been receiving lysivane and stramonium. In four cases an improvement was noted in their speech—one might say a distinct improvement.
5. The mental state of the patients was satisfactory but a specific euphoriant effect could not be proved. It was noted that five patients stated that they preferred Disipal to their previous medicines.

It is obvious that no one drug can be expected to be successful in every case and that the best one to use is often a matter of experiment. If present trends continue it seems likely that orphenadrine will establish itself as a standard drug in the treatment of Parkinsonism either by itself or in suitable combinations.

#### SUMMARY.

The symptoms of eleven out of twelve patients suffering from Parkinsonism with associated mental symptoms were controlled in a satisfactory manner and improvement was noted in articulation in several cases when compared with their previous drugs. Side effects were slight and no toxic signs were found. The mental state was satisfactory and some patients expressed a preference for the drug. It appears to be as efficacious as other more commonly employed anti-Parkinson agents.

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